



Febrile Nonhemolytic Transfusion Reactions

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Definition

- A. Febrile nonhemolytic transfusion reactions (FNHTRs) are the development of an otherwise unexplained temperature increase of $\geq 1^{\circ}\text{C}$ or 2°F from baseline or the onset of chills or rigors in a patient who is receiving a transfusion.
- B. FNHTRs also may develop in patients who have completed a transfusion within the past four to six hours.

Incidence

- A. FNHTRs are reported in 0.5%–5% of all transfusions.
- B. FNHTRs are the most common complication of platelet transfusion.
 1. Incidence ranges from 1.7% to 31%.
 2. Higher incidences are seen in patients who have received multiple prior transfusions.
- C. Incidence may decrease with increased use of prestorage leukocyte-reduced blood products.
- D. Higher incidence of blood transfusion reactions occurs in patients with hematologic and malignant diseases.

Risk Factors

- A. Previous transfusion
- B. Prior pregnancy
- C. History of previous FNHTR
- D. History of hematologic disorder or malignancy

Pathophysiology

- A. Reaction is mediated by donor leukocytes and cytokines.

1. Transfusion recipient develops antibodies to human leukocyte antigens (HLAs) from prior exposure via previous transfusion or prior pregnancy. This process is called alloimmunization.
2. Recipient reacts to
 - a. HLAs on donor platelets and leukocytes
 - b. Platelet-specific antibodies.
3. The presence of donor leukocytes in transfused red blood cells and platelets is a major contributor to the development of refractoriness and alloimmunization in patients who have received multiple transfusions.
4. Cytokines are produced and accumulated during the storage of blood products by the leukocytes that contaminate red blood cell and platelet concentrates.
 - a. One unit of red blood cells contains approximately 1–2 billion leukocytes.
 - b. One unit of random donor platelets contains about 50 million leukocytes.
 - c. One unit of pheresed platelets contains between 1 million and 1 billion leukocytes.

- B. Macrophages, lymphocytes, and endothelial cells secrete cytokines.
- C. Leukocytes in platelet concentrates stored at room temperature generate and release pyrogenic cytokines that may directly cause febrile reactions.
 1. Transfusion of cytokines that have developed during storage is a major factor in platelet transfusion reactions.
 - a. Interleukin-1 β (IL-1), IL-6, IL-8, and tumor necrosis factor- α

- have been measured in platelet supernatant.
- b. IL-1, IL-6, IL-8, and tumor necrosis factor- α mediate inflammatory responses and may act as direct pyrogens.
- c. Cytokines appear to be transfused with the plasma component of the blood product.
2. FNHTRs in red blood cell transfusions primarily are the result of HLA incompatibility of the donor leukocytes, which contaminate the red blood cell product.
- D. Leukoreduction removes more than 99.9% of leukocytes from cellular blood components.
- E. Reducing the number of leukocytes transfused with blood products can decrease incidence of FNHTRs.
 1. Blood products labeled as “leukocyte reduced” must meet certain criteria for maximum residual leukocyte content.
 - a. Red blood cells— 1.0×10^6
 - b. Platelets, pheresis— 1.0×10^6
 - c. Platelets— 1.6×10^5 per unit. Four to six units of pooled platelets must contain $\leq 1.0 \times 10^6$ residual leukocytes.
 2. The U.S. Department of Health and Human Services’ Advisory Committee on Blood Safety and Availability recommended in February 2001 that universal prestorage leukoreduction of all nonleukocyte cellular blood components

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